REMARKS

Claims 94 and 99-107 were pending in the application. Independent claims 94 and 99 have been amended to delete reference to "conservative sequence modifications." Support for this amendment is available throughout the specification and claims as originally filed.

The foregoing amendments should in no way be construed as an acquiescence to any of the Examiner's rejections, and have been made solely to expedite examination of the present application and to place the pending claims in better condition for appeal. No new issues have been raised and no additional search should be required. Accordingly, Applicants respectfully request that the foregoing claim amendments be entered after final. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s). *No new matter has been added.*

Rejection of Claims 94 & 99-107 Under 35 U.S.C. §112, First Paragraph

Claims 94 and 99-107 are rejected as containing new matter. Specifically, the Examiner alleges that "the specification and the claims as originally filed do not provide support for the invention as now claimed." Applicants address each of the individual issues raised by the Examiner below.

A) With respect to claim 94, the Examiner asserts that " . . . the specification does not adequately describe antibodies comprising the claimed CDRs."

First, Applicants note that the Examiner's current characterization of the subject matter of claim 94 is incorrect. Claim 94 is drawn to a human antibody (and binding portions thereof), which binds human dendritic cells and comprises specific heavy and light chain CDR1, CDR2 and CDR3 sequences. Further, as amended above, "conservative sequences modifications" have been removed from claim 94.

Support for amended claim 94 can be found throughout the specification as originally filed. For example, the presently claimed CDRs are present in the full-length variable regions provided in SEQ ID NOs:2 and 4, as originally filed. These CDRs were readily identifiable by one of ordinary skill in the art at the time of filing using standard techniques. For example, by using the Kabat and the Clothia numbering schemes (widely adopted standards in the art at the

time of filing) the CDRs and constant regions could have been determined simply by reviewing the sequence information provided by Applicants, *e.g.*, by plugging this sequence information into a computer program, such as, *e.g.*, SUBIM (a program for analyzing the Kabat database and determining the variability subgroup of a new immunoglobulin sequence, S. Deret, C. Maissiat, P. Aucouturier and J. Chaomillier, CABIOS, vol. 11, no. 4, 1995, Pages 435-439; enclosed as Appendix A), which automatically identifies the CDRs and constant regions. Therefore, the CDRs recited in claim 94 do not constitute new matter. They are a readily identifiable feature of the full-length variable regions, as originally filed.

Applicants respectfully point out that the express description of an *inherent property*, such as *physical structure*, does not constitute new matter and can be added to the specification with effect as of the original filing date. *See In re Nathan*, 51 C.C.P.A. 1059, 328 F.2d 1005, 1008-09, 140 U.S.P.Q. (BNA) 601, 604 (CCPA 1964) (amendment which defines more precisely an inherent characteristic of the claimed subject matter for those skilled in the art is not new matter); *In re Reynolds*, 58 C.C.P.A. 1287, 443 F.2d 384, 170 U.S.P.Q. (BNA) 94 (CCPA 1971) (application may be later amended to recite inherent feature of claimed invention, without introducing prohibited new matter); *Kennecott Corp. v. Kyocera International, Inc.*, 835 F.2d 1419, 1422, 5 USPQ2d 1194, 1197 (Fed. Cir. 1987) (subsequent inclusion of existing physical structure to describe inherent feature is not new subject matter), cert. denied, 486 U.S. 1008 (1988). In sum, an amendment which is made to clarify or further describe inherent features or structural properties is permissible and does not constitute new matter.

Analogous to the facts of the foregoing decisions, since the CDRs recited in claim 94 are an *inherent* and recognizable portion of the variable region *structure,* the recitation of the CDRs in claim 94 does not constitute new matter.

Applicants also traverse the Examiner's assertion that antibodies comprising the claimed CDRs in other framework regions is new matter. Indeed, such antibodies are clearly contemplated by the present specification. In this regard, Applicants respectfully note that that which is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. *See In re Hayes Microcomputer Products Inc. Patent Litigation*, 982 F.2d 1527, 1533, 25 USPQ2d 1241, (Fed. Cir. 1992) (noting exact description of subject matter is not necessary, as long as "persons of ordinary skill in the art recognize" that applicant invented what is claimed); *In re Lukach*, 442 F.2d 967, 969, 169 USPQ 795 (CCPA 1971) (an invention need not be

described in *ipsis verbis* to satisfy description requirement of 35 U.S.C. § 112); *In re Wertheim*, 541 F.2d 257, 262 and 265, 191 USPQ 90 (CCPA 1976) ("lack of literal support" is insufficient to support a rejection under 35 U.S.C. § 112), appeal after remand 646 F.2d 527, 209 USPQ 554 (CCPA 1981); and MPEP § 2163.

As applied to the presently claimed invention, it was well-known in the art that antibodies interact with target antigens predominantly through amino acid residues that are located in the six heavy and light chain complementarity determining regions (CDRs). For this reason, the amino acid sequences within CDRs are more diverse among individual antibodies than sequences outside of CDRs (*e.g.*, the framework sequences). Because CDR sequences are responsible for most antibody-antigen interactions, it was also known that recombinant antibodies which mimic the properties of specific naturally occurring antibodies could be generated by constructing expression vectors that include CDR sequences from the specific naturally occurring antibody grafted onto framework sequences from any number of antibodies (see, *e.g.*, Riechmann, L. *et al.* (1998) *Nature* 332:323-327 (enclosed as Appendix B); Jones, P. *et al.* (1986) *Nature* 321:522-525 (enclosed as Appendix C); Queen, C. *et al.* (1989) *Proc. Natl. Acad. See. U.S.A.* 86:10029-10033 (enclosed as Appendix D); U.S. Patent No. 5,225,539 to Winter, and U.S. Patent Nos. 5,530,101; 5,585,089; 5,693,762 and 6,180,370 to Queen *et al.*).

It was also well-known that DNA fragments encoding the V_H and V_L segments of a particular antibody can be further manipulated by standard recombinant DNA techniques to convert the variable region genes to full-length antibody chain genes, to Fab fragment genes or to a scFv gene. In these manipulations, a V_L- or V_H-encoding DNA fragment is operatively linked to another DNA fragment encoding another protein, such as an antibody constant region and/or a flexible linker. For example, with respect to the DNA encoding the V_H region, this DNA can be converted to a full-length heavy chain gene by operatively linking the V_H-encoding DNA to another DNA molecule encoding human heavy chain constant regions (CH1, CH2 and CH3). The sequences of such human heavy chain constant region genes were also well-known in the art (see *e.g.*, Kabat, E. A., *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242) and DNA fragments encompassing these regions were readily obtainable by standard PCR amplification. For example, the heavy chain constant region can be, *e.g.* an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD constant region. For a Fab fragment heavy chain gene, the V_H-

encoding DNA can be operatively linked to another DNA molecule encoding only the heavy chain CH1 constant region.

Similarly, it was also known that the isolated DNA encoding the V_L region can be converted to a full-length light chain gene (as well as a Fab light chain gene) by operatively linking the V_L-encoding DNA to another DNA molecule encoding the human light chain constant region, CL. The sequences of human light chain constant region genes were also known in the art (see *e.g.*, Kabat, E. A., *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242) and DNA fragments encompassing these regions were readily obtainable by standard PCR amplification. For example, the light chain constant region can be, *e.g.*, a kappa or lambda constant region.

Moreover, to create a scFv gene, as taught in the present specification (for example, in Figure 9 and at page 11, lines 10-19), the V_H- and V_L-encoding DNA fragments can be operatively linked to another fragment encoding a flexible linker, *e.g.*, encoding the amino acid sequence $(Gly_4\text{-}Ser)_3$, such that the V_H and V_L sequences can be expressed as a contiguous single-chain protein, with the V_H and V_L regions joined by the flexible linker (see *e.g.*, Bird *et al.* (1988) *Science* 242:423-426 (enclosed as Appendix E); Huston *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883 (enclosed as Appendix F); McCafferty *et al.*, (1990) *Nature* 348:552-554 (enclosed as Appendix G)).

Therefore, the subject matter that the Examiner asserts is new matter was conventional in the art and need not be disclosed. Accordingly, the pending claims do not recite new matter.

B) With respect to the Examiner's rejection of claims 95-98, this rejection is moot since claims 95-98 are no longer pending in the current application.

With respect to claims 100-107, as they depend from claim 94, Applicants respectfully traverse for the reasons set forth above.

C) With respect to claim 99, Applicants respectfully note that this claim no longer refers to "conservative sequence modifications." Moreover, support for amended claim 99, which is drawn to an isolated human monoclonal antibody (or antigen binding portion thereof) that binds to human dendritic cells and has particular human heavy and light chain variable

region amino acid sequences (*i.e.*, SEQ ID NOs: 4 and 2, respectively), can be found throughout the specification as originally filed, *e.g.*, Figure 13 and original claim 51.

D) With respect to claims 100-107, as they depend from claim 99, Applicants respectfully traverse for the reasons set forth above.

Rejection of Claims 94 & 99-107 Under 35 U.S.C. §112, First Paragraph- Written Description

Claims 94 and 99-107 are rejected as not meeting the written description requirement with regard to "conservative sequence modifications."

Applicants respectfully traverse this rejection. However, to expedite prosecution, Applicants have amended claims 94 and 99 so that these claims no longer refer to "conservative sequence modifications", thereby rendering this rejection moot.

Rejection of Claims 94 & 99-107 Under 35 U.S.C. §112, First Paragraph- Enablement

Claims 94 and 99-107 are rejected as not being enabled because, according to the Examiner, "the claims recite no limitations on the number of amino acids that can be 'modified' and "no examples of modified antibodies…are disclosed."

Applicants respectfully traverse this rejection. However, as indicated above, to expedite prosecution, Applicants have amended claims 94 and 99 so that these claims no longer refer to "conservative sequence modifications." Therefore, this rejection is now moot.

CONCLUSION

Based on the foregoing amendments and arguments, reconsideration and withdrawal of all the rejections, and allowance of this application with all pending claims are respectfully requested. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 12-0080, under Order No. CDJ-166RCE.

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Respectfully submitted,

By _____

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